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Medical Officer's Review of NDA 21-117

Applicant: Abbott Laboratories
Contact: Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
847-937-5513

Submission/review dates
Date of Submission: 4/9/99
CDER stamp date: 3/31/99
Date submission received by reviewer: 4/15/99
Date review begun: 4/15/99
Date review completed: 1/14/00; revised 1/18/00

Drug Identification
Generic name: **Calcium Chloride 10% Injection, USP, in Plastic Syringe**
Proposed trade name: **Calcium Chloride 10% Injection, USP, in Plastic Syringe**
Chemical name: Calcium Chloride
Molecular formula: $CaCl_2$
Molecular weight: 111 g/mol anhydrous (147.02 g/mol dihydrate form)

Pharmacologic Category: small volume parenteral

Route of Administration: intravenous injection

Proposed Indication and Usage : treatment of hypocalcemia

Proposed Dosage and Administration: 200 mg to 1 gram slow intravenous injection – not to exceed 1 ml/min

Related Drugs: other parenteral calcium-containing solutions (see list in text); 25% dextrose injection in 10 ml plastic syringe (NDA 19-445/s-004 & 006)

Material Reviewed: NDA 21-117 vol. 1- 6; Amendment (4/12/99); Additional journal articles and book chapters obtained by review of Medline and cited references

Regulatory Recommendation:

Approval for the indication "treatment of hypocalcemia in those conditions requiring a prompt increase in plasma calcium levels" only, pending change in labeling, as requested by FDA.

Summary

Abbott Laboratories currently markets a calcium chloride 10% injection in a glass syringe under the brand name ABBOJECT (R). Since this product was on the market in 1938, it was "grandfathered" under the 1938 Food, Drug and Cosmetic Act. The current submission is for calcium chloride 10% injection in a 10 ml Ansyr (R) plastic syringe. The sponsor provides correspondence from Roger L. Williams, M.D., Deputy Center Director for Pharmaceutical Science, Center for Drug Evaluation and Research, FDA (9/3/96) and Murray M. Lumpkin, M.D., Deputy Center Director (Review Management), Center for Drug Evaluation and Research, FDA (11/6/98) to support the literature - based 505(b)(2) NDA submission. [A copy of the correspondence is attached in the Appendix.]

Calcium Chloride, USP, 10% is listed as a product for which there is no approved reference listed drug and therefore approval under section 505(b) of the Food, Drug and Cosmetic Act was required prior to marketing in a new plastic prefilled syringe, in Dr. Williams' letter. Dr. Lumpkin cited CDER MAPP 6020.2 "Applications for Parenteral Products in Plastic Immediate Containers" that drug products contained in plastic are deemed by regulation (21 CFR 310.502 (a) (10) and 310.509(a)) to be "new drugs". In addition, he noted "Based on your description of the products, including the apparent substantial marketing history, you should consider whether an application under section 505(b)(2), which may sometimes may consist of simple literature/medical textbook information to support safety and efficacy, may be feasible for each of theses drug products."[sic]

Thus, the sponsor has submitted references from a literature review from 1966 to January 1999 using Medline database, a manual search from 1965 to 1937, and medical textbook references to search the keywords "calcium chloride – administration, dosage, toxicity, therapeutic use and clinical use" to support the indications. The sponsor requests the following indications (as currently listed on the grandfathered product in a glass syringe): "10% Calcium Chloride Injection, USP, is currently indicated for the treatment of hypocalcemia in those conditions requiring a prompt increase in blood plasma calcium levels

Furthermore, the label text in the submission recommends that 10% Calcium Chloride Injection, USP, "be administered by slow intravenous injection (not to exceed 1 ml/min) and/or in cardiac resuscitation by injection into the ventricular cavity. The usual adult dose in hypocalcemic disorders ranges from 500 mg to 1 g at intervals of 1 to 3 days. In magnesium intoxication, an initial adult dose of 500 mg should be administered promptly and the patient observed for signs of recovery before further doses are given. In hyperkalemic ECG disturbances of cardiac function, the dosage of calcium chloride injection should be titrated by constant monitoring of ECG changes during administration. In cardiac resuscitation, the usual adult dose ranges from 500 mg to 1 g intravenously, or from 200 mg to 800 mg when injected into the ventricular cavity."

The medical officer has reviewed the sponsor's submitted indications and literature as well as other current guidelines and textbooks regarding cardiac resuscitation and indications for calcium chloride, which were not submitted by the sponsor. Of note, the approval of 10% calcium chloride injection for the treatment of hypocalcemia is based more on current standards of medical practice rather than on any large randomized, placebo-controlled, double blind clinical trials, which are not available and if performed not published. In analysis of the available data and potential benefits and risks of the use of the drug product 10% calcium chloride injection in a plastic syringe, the reviewer recommends approval of calcium chloride for the hypocalcemia indication only.

10% Calcium Chloride – Definition of Calcium Content

10% Calcium Chloride injection consists of 1 gram of calcium chloride in a 10 ml syringe, or 100 mg/ml. This concentration represents 27 mg or 1.4 Meq of elemental calcium per ml. Thus, one 10 ml syringe provides 270 mg of elemental calcium. There is a possible dosage confusion, as the dosage recommendation in various texts and reviews is given either as amount of calcium chloride or amount of elemental calcium, and often it is not specified. In addition, calcium chloride and elemental calcium recommendations are not usually cross-referenced to each other.

Other Approved Calcium Chloride Solutions

The drug product calcium chloride occurs naturally in the environment and in human physiology. Calcium is essential for nerve conduction, muscular contraction, and blood coagulation. It functions as an enzyme cofactor and affects secretion of endocrine and exocrine glands. The drug product calcium chloride is not patentable. Currently four solutions containing calcium chloride are approved by the FDA for injection and/or infusion, as outlined below. [Summary is from the DSS system listing.] None has the same concentration of active ingredient as this 10% solution. Of note, none is approved for the treatment of hypocalcemia.

NDA Number (Division, Date Approved)	Drug Name (Sponsor)	Indication(s)
19718 (600, 9/29/89)	Multiple Electrolytes Injection Type 2 (B Braun)	Source of electrolytes and water for hydration; an alkalinizing agent
19933 (170, 8/29/89)	Calcium chloride/potassium chloride etc (Baxter Healthcare)	Create regional hypothermia to reduce and minimize manifestations of warm temperature ischemia
20002 (600, 4/17/92)	Ringer's Injection (B Braun)	Source of electrolytes and water for hydration
20163 (110, 12/4/92)	Calcium chloride/ dextrose /Mag Cl /NaCL/N (Baxter Healthcare)	Continuous ambulatory peritoneal dialysis

Medical Literature References Provided by the Sponsor

The sponsor has provided copies of 22 references to support the above four indications. [See list "MEDICAL LITERATURE REFERENCES 10% Calcium Chloride" in the Appendix.] Two references are clinical studies and are discussed in more detail in the discussion of the specific indications (see below). Twenty references are reviews, book chapters, or tabular excerpts from book chapters. The two cited clinical studies are small, single center studies and do not meet the usual FDA standards of large, multicenter, double-blind, randomized clinical trials. The textbook chapters and reviews summarize and reiterate various indications, doses, and risks of calcium chloride. However, these comments are based primarily on standard of care with rare references to published clinical studies.

The currently recommended indications and dosages for intravenous calcium chloride in emergency cardiac care are summarized in the table below. Some of these references are abstracted from the sponsor's submission; additional references have been selected by the medical officer. The sponsor's indications and recommended dosages are included for comparison.

Indication	**Dosage of $CaCl_2$**	**Source***
Hypocalcemia	**200 mg to 1 gm by slow intravenous injection (not to exceed 1 ml/min) or by injection into the ventricular cavity**	**Abstracted from NDA label**
Hypocalcemia	8-16 mg/kg 10% solution; repeat if necessary	*Advanced Cardiac Life Support, American Heart Association, 1997 (The sponsor submitted an excerpt from the 1994 edition, which had the same recommendation.)
Hypocalcemia	2-4 mg/kg of 10 % solution; repeat as necessary at 10 minute intervals	*Guidelines for CPR, JAMA 268(16):2209-10; 10/28/92
Documented hypocalcemia,	20 mg/kg of $CaCl_2$ (0.2 ml/kg of 10% solution); repeat in 10 minutes if needed, based on ionized calcium concentration	Rosen P, ed., Emergency Medicine, 4th ed, Mosby, 1998
Hypocalcemia	• 2 ml of 10% solution of $CaCl_2$ (2-4 mg/kg); bolus may be repeated at 10 min.	*Civetta JM, Taylor RW, Kirby RR Critical Care, 3rd ed, pp. 505 & 2268, Lipincott-

APPEARS THIS WAY ON ORIGINAL	intervals - or • 90 mg elemental calcium loading dose (1 g = 272 mg [4.65 mMol] Ca); 0.5-2.0 mg/h, adjusted to ionized calcium concentration	Raven, 1997 APPEARS THIS WAY ON ORIGINAL
Hypocalcemia crisis (e.g. neonatal tetany and tetany due to parathyroid deficiency, vitamin D deficiency, and alkalosis), prevention of hypocalcemia during exchange transfusions,	500 mg to 1 g at intervals of 1-3 days; for hyperkalemia, according to ECG APPEARS THIS WAY ON ORIGINAL	*Ornato JP, Gonzales ER Drug Therapy in Emergency Medi cine, Churchill Livingstone, pp. 373-4, 1990 APPEARS THIS WAY ON ORIGINAL

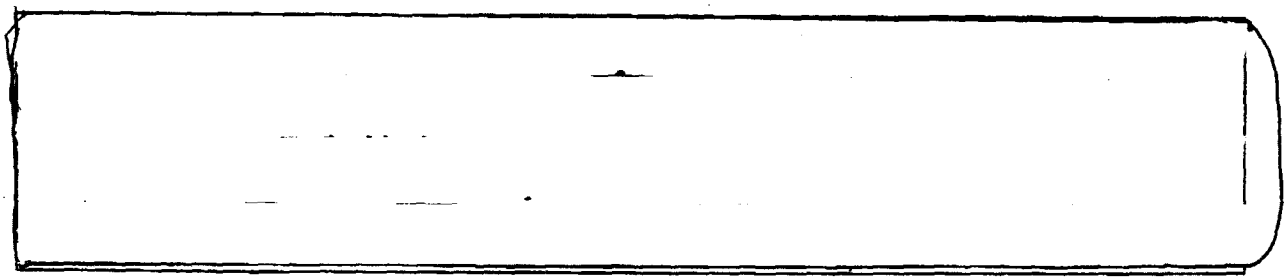
* References selected by the medical officer rather than the sponsor are marked by (*).

As can be seen from this table, there is a range of dosages and a potentially broad range of indications. However, the authors do not cite any reference studies for dosage selection, which appears to be somewhat anecdotal and empirical. It is important to stress that ionized and not total calcium concentrations be measured in the acute settings.

Additional Literature Search per Medical Officer

The medical officer reviewed references cited by the sponsor's references that could provide further justification for the sponsor's requested indications. In addition, the medical officer performed several Medline searches to elicit additional references for these indications. The general approach was a search for references common to both calcium chloride and the specific indication. 'Clinical trial' was also added as a third term; however, with the addition of the clinical trial term, even less references were found.

Number of References Identified Per Medline Search		
Indication	Indication + Calcium Chloride**	Indication + Calcium Chloride + Clinical Trial
Hypocalcemia	99	1



Admittedly, this search approach is simplistic, but it emphasizes the paucity of clinical trial data to support the requested indication

FDA Guidance Regarding Submission of 505 (b) 2 NDAs

Applications that may be considered under Food, Drug and Cosmetic Act section 505(b)(2) include (1) applications that rely in part upon published literature and (2) applications that rely in part upon the agency's finding of safety and effectiveness for an approved drug. These applications are expected to contain adequate evidence of safety and effectiveness, as outlined in the draft guidance "Applications Pursuant to 505(b)(2)". The guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (May 1998, page 19) describes specific factors that "increase the possibility of reliance on published reports alone to support approval of a new product or new use", as quoted below:

a) "Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.
b) A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
c) Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g, overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more objective endpoints such as cause-specific mortality or relief of symptoms.
d) Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).
e) Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively."

The application for calcium chloride injection does not clearly meet the expectation of this guidance.

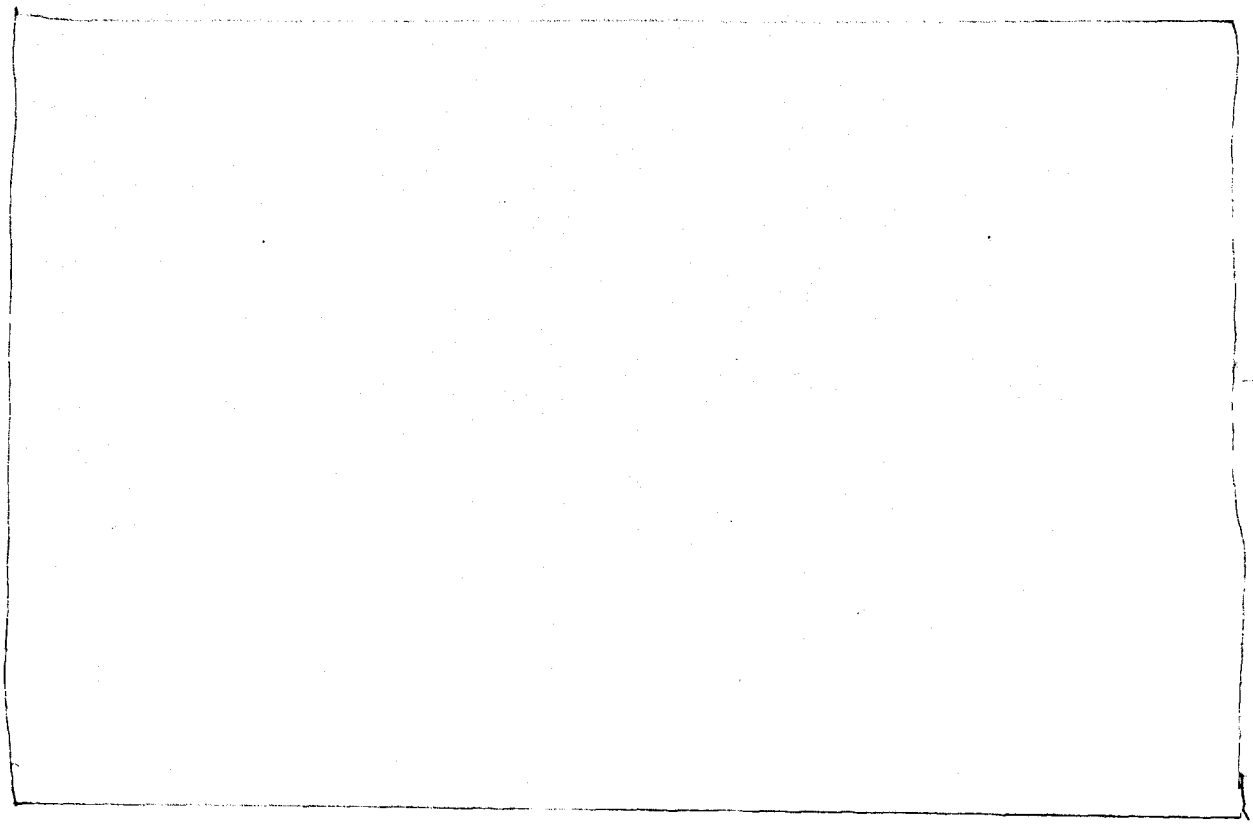
Evidence from Clinical Studies for Requested Indications

In the following section, the evidence from clinical studies is evaluated for each of the sponsor's proposed indications.

Indication #1: *treatment of hypocalcemia in those conditions requiring a prompt increase in blood plasma calcium levels*

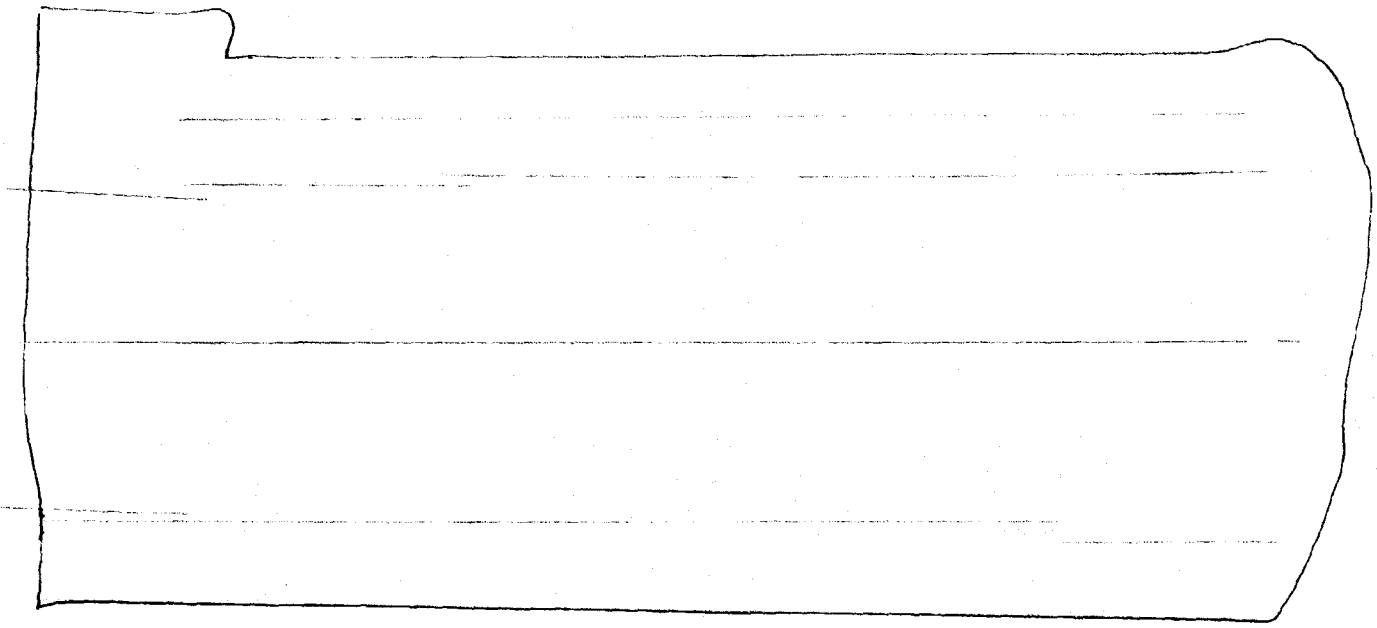
The sponsor cites the study by Broner C et al, "Clinical and laboratory observations: a prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children" (Journal of Pediatrics 1990: 117:986-989). 37 critically ill pediatric patients were randomized to receive calcium chloride (n=17) or calcium gluconate (n=20) through central venous catheters, receiving 0.136 mEq elemental calcium per kg per dose. Ionized calcium levels were obtained before and 30 minutes after administration of the calcium salt and increased from 1.03 $\pm$ 0.14 to 1.22 $\pm$ 0.12 and from 1.07 $\pm$ 0.12 to 1.16 $\pm$ 0.09 mmol/L in the two groups, respectively ($p<0.05$ for each comparison). This study was designed to compare the two calcium formulations, and there is no control group. Presumably, calcium concentration would be unchanged without additional calcium. Thus, this study suggests that calcium chloride acutely increases the calcium concentration.

The only clinical trial for the hypocalcemia indication identified by the medical officer's Medline search was the reference Cote CJ et al "Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: effects of infusion rate, duration, and treatment with calcium chloride" (Anesth Analg 1988, 67(2): 152-60). Twenty eight thermally injured anesthetized pediatric patients with massive blood loss were infused with fresh frozen plasma at different rates. The subsequent rapid reductions in ionized calcium were reduced when calcium chloride was administered. This study is not blinded and comprises a small number of subjects. However, it confirms that exogenous calcium chloride administration raises calcium concentrations acutely.



Safety Concerns:

In the transition of packaging 10% calcium chloride in a plastic



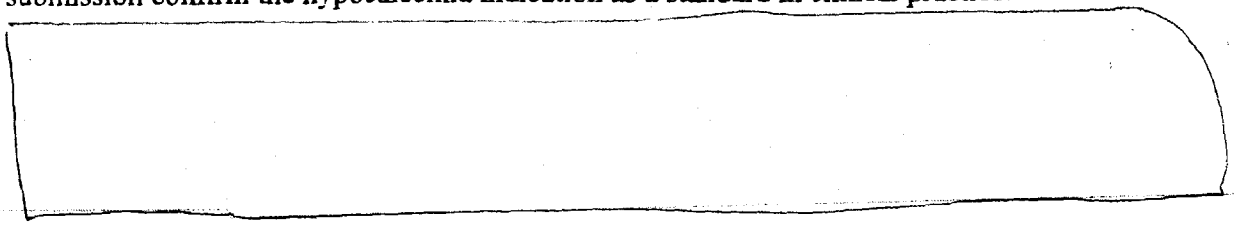
Other Safety Concerns

The literature cites bradycardia, peripheral vasodilatation, decrease in blood pressure, and severe local necrosis, sloughing, abscess formation from intramuscular or subcutaneous use. Digitalis glycosides may precipitate arrhythmias. Calcium chloride may antagonize effect of verapamil. Overdosage or toxicity with calcium chloride manifests with the signs and symptoms of acute hypercalcemia: fatigue, weakness, confusion, anorexia, nausea, vomiting, polyuria, ECG changes, bradycardia.

Assessment of Efficacy and Safety of Calcium Chloride

Calcium chloride 10% injection in a glass syringe has been available for over 60 years. The transition to a plastic syringe has required the meeting of exacting chemistry standards to assure safety and efficacy (see chemistry review). However, the sponsor has not provided convincing clinical data from the literature to support the indications in its proposed label. In fact, some of the sponsor's references actually questioned or negated the validity of the requested indications, as discussed above. The paucity of clinical trial data for this drug product thus raises consideration about the approval of a drug product, albeit a "grandfathered" product, if there are insufficient data to support safety and efficacy according to current FDA guidances.

For the hypocalcemia indication, the data provided by the sponsor indicate that calcium chloride raises calcium concentrations, thus supporting efficacy regarding the indication of hypocalcemia requiring a prompt increase in blood calcium levels. The study presented is small, there is no control group, and the actual data have not been included in the submission. Other clinical studies reviewed by the medical officer and the textbook and review references in the NDA submission confirm the hypocalcemia indication as a standard in clinical practice.



These approval and non-approval recommendations evolve from current FDA guidances, to assure some consistency in the bases for indications across drug products. The submitted basis of approval of calcium chloride is modest. However, the approval of calcium chloride for the acute hypocalcemia indication assures the chemical safety of a centrally infused product, with respect to standards of precise dosage, stability, pyrogenicity, and purity. This product is widely used clinically and can be potentially life-saving. The clarification of the dosage of calcium chloride versus elemental calcium in the label are essential for the practicing physicians and other healthcare workers. The sponsor is encouraged to submit additional studies with adequate statistical power to expand the indication for this drug product.

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Labeling Recommendations

A corrected "red-line" version of the sponsor's label was sent to the sponsor in December 1999. The recommended changes are also highlighted in the summary below.

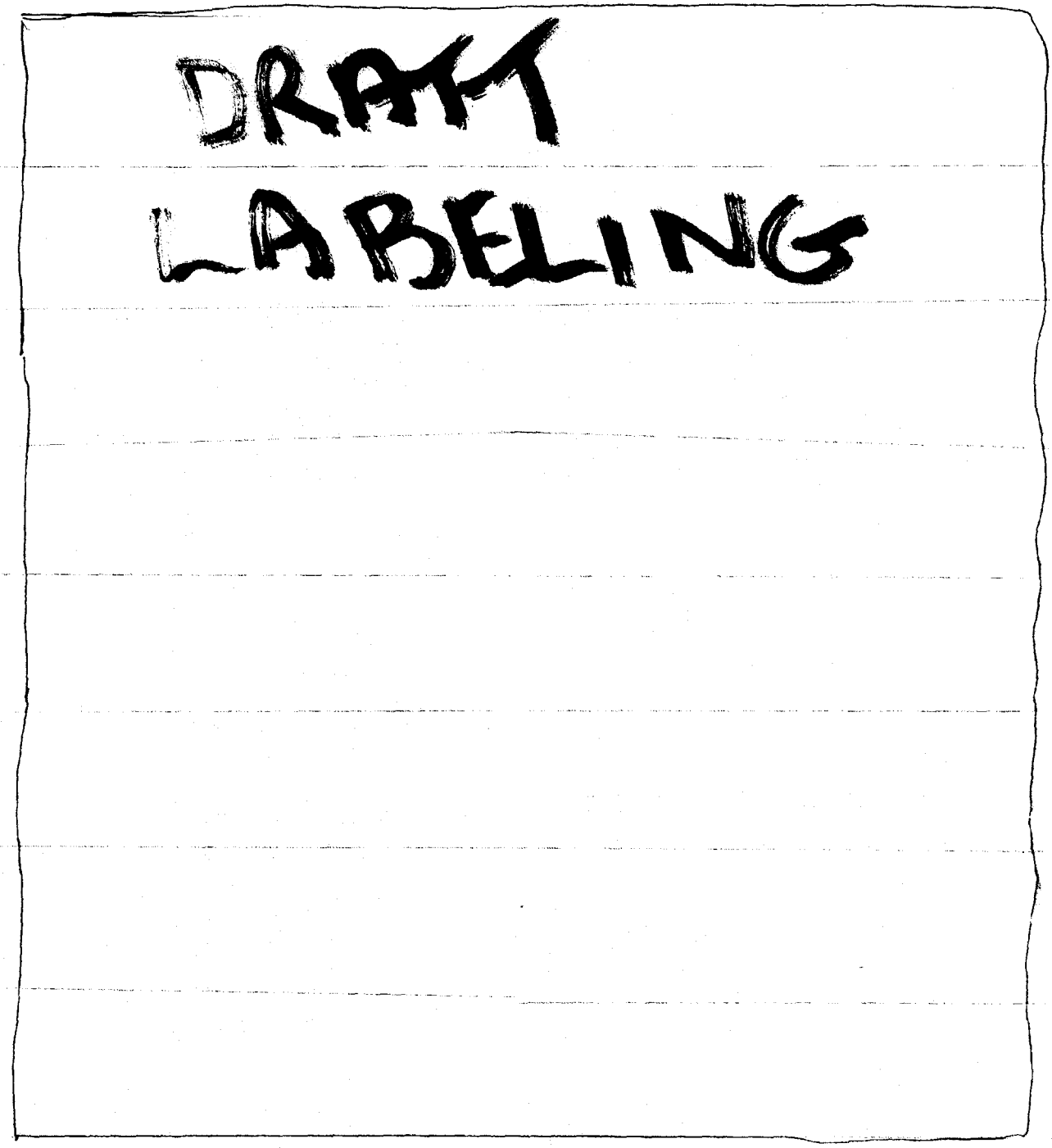
DRAFT

LABELING

Further consideration of the label in the context of the paucity of clinical supporting data in the NDA submission and current FDA guidances prompts the simplification of the indication to hypocalcemia only and the emphasis of the dosage of calcium chloride versus elemental calcium.

The following changes were discussed with the sponsor on 1/18/00 in a telephone conversation:

DRAFT LABELING



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DRAFT

LABELING

Recommendations

Approval for the indication "Treatment of hypocalcemia in those conditions requiring a prompt increase in plasma calcium levels" only, pending change in labeling, as requested by FDA.

/S/

Joanna K. Zawadzki, M.D., F.A.C.P.
Medical Officer
Division of Metabolic and Endocrine Drug Products

APPEARS THIS WAY
ON ORIGINAL

Concurrence:

/S/ 11/21/00

Eric Colman, M.D.
Acting Team Leader
Division of Metabolic and Endocrine Drug Products

John K. Jenkins, M.D.
Acting Division Director, DMEDP
Director, ODE II

The initial labeling recommendation in this review was discussed with Gloria Troendle, M.D. in December 1999 prior to her retirement.

Appendixes:

9/3/96 Letter from Roger L. Williams, M.D., Deputy Center Director for Pharmaceutical Science, Center for Drug Evaluation and Research, FDA

11/6/98 Letter from Murray M. Lumpkin, M.D., Deputy Center Director (Review Management), Center for Drug Evaluation and Research, FDA

Sponsor's MEDICAL LITERATURE REFERENCES 10% Calcium Chloride

Distribution:

Archival:HFD580/NDA21-117
HFD510/Jenkins/Colman/McCort/Lewis/Shore/Malozowski/Zawadzki

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ON ORIGINAL

ATTACHMENT I

1. LETTER FROM DR. ROGER WILLIAMS TO DR. THOMAS WILLER, ABBOTT LABORATORIES, DATED SEPTEMBER 3, 1996, ITEMIZING THE SUBMISSION STATUS OF PROPOSED PRODUCTS.

2. LETTER FROM DR. MURRAY LUMPKIN TO DR. THOMAS WILLER, ABBOTT LABORATORIES, DATED NOVEMBER 6, 1998, PROVIDING GUIDANCE FOR GAINING MARKETING APPROVAL FOR CHANGING CERTAIN PARENTERAL DRUG PRODUCTS FROM GLASS TO PLASTIC SYRINGE CONTAINERS.

   (ATTACHMENT: CDER MAPP 6020.2 "APPLICATIONS FOR PARENTERAL PRODUCTS IN PLASTIC IMMEDIATE CONTAINERS")

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Thomas F. Willer, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
Abbott Laboratories
Dept. 389, AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

SEP 3 1996

RE: Applications for Products in New Plastic Syringes

Dear Dr. Willer:

This responds to your inquiry to Dr. Marilyn Apfel concerning the types of applications that should be submitted for approval of certain drug products that you propose to package in prefilled syringes made of a new plastic material.

We have applied the following general policies in reaching the decisions outlined below for each individual product:

1. Applications for approval of small volume parenteral (SVP) products to be packaged in new plastic syringes may be submitted as ANDAs under section 505(j) or AADAs under section 507 of the Federal Food, Drug, and Cosmetic (FD&C) Act if there is an approved reference listed drug product in the current edition of the publication Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book), and provided that approval of the product does not require studies beyond limited confirmatory testing. Limited confirmatory testing means simple studies intended to rule out unlikely problems. In some cases limited confirmatory testing may include acute animal studies. However, a study to answer basic safety or effectiveness questions or a study that would require substantial scientific review would not be considered limited confirmatory testing. If there are toxicology issues associated with the new previously unapproved plastic that require animal studies beyond limited confirmatory testing or the testing described in the USP to show that the drug product is safe, then an abbreviated application under section 505(j) or section 507 is not appropriate, and an NDA or supplement under section 505(b) or section 507 should be submitted. The concentration and total volume of the proposed product must be the same as for the approved product.

2. If you have an approved ANDA for a product packaged in vials or ampules, a separate ANDA is required for approval of that product packaged in a prefilled syringe.

3. Separate ANDAs are required for each container material (glass and plastic).

4. If Abbott holds an approved NDA for the same product in a different container, a supplement to the NDA should be submitted for the product in the new plastic syringe.

We have reviewed the list of products you provided to Dr. Marilyn Apfel in your October 31, 1994, letter. We have added Iopamidol Injection, USP, 51%, and Verapamil Hydrochloride Injection, USP, 10 mg/mL, to the list based on your February 15, 1996, telephone conversation with Mr. Thomas Hassall. We have separated the products into three groups: 1) products for which Abbott currently holds an approved NDA or ANDA for marketing the products in a vial or in a prefilled syringe made of either glass or a different plastic material; 2) products for which Abbott does not currently have approved NDAs or ANDAs but for which a reference listed drug exists; and 3) products for which there is no approved reference listed drug. Our conclusions concerning the appropriate type of application to be submitted for each product you proposed are summarized below. ANDAs may be submitted, where recommended, below provided there are no toxicology issues associated with the new plastic that require animal studies beyond limited confirmatory testing or the testing described in the USP to show that the product is safe.

1. **Products for which Abbott holds approved NDAs or ANDAs:**

a. Bretylium Tosylate Injection, USP, 50 mg/mL

Abbott's NDA 19-030 is approved for marketing Bretylium Tosylate Injection, USP, 50 mg/mL in a 10 mL, plastic vial. The proposed product in the new plastic syringe should be submitted as a supplemental application to this NDA.

b. Furosemide Injection, USP, 10 mg/mL

Your application, number 18-667, is an ANDA under which you have approval to market Furosemide Injection, USP, 10 mg/mL, in prefilled glass syringes. Under present policy, you should submit a separate ANDA for approval of Furosemide Injection, USP in the new plastic syringe.

c. Lidocaine HCl Injection, USP 1%

ANDA 88-299 is approved for marketing Lidocaine HCl Injection, USP 1% in 20 mL, 30 mL, and 50 mL plastic vials. A separate ANDA should be submitted for approval of Lidocaine HCl Injection, USP, 1% in the new prefilled plastic syringe.

d. Lidocaine HCl Injection, USP 2%

ANDA 83-158 provides for marketing this product in the Abboject® glass syringe and the "Universal Additive Syringe," also a glass package. Because the proposed product is to be packaged in a plastic syringe, our present policy requires you to submit a new ANDA.

e. Sodium Chloride Injection, USP, 0.9%

Abbott's NDA 19-218 is approved for marketing 0.9% Sodium Chloride Injection, USP, in plastic syringes. You should submit a supplemental application to NDA 19-218 for the proposed product in the new plastic syringe.

f. Sterile Water for Injection

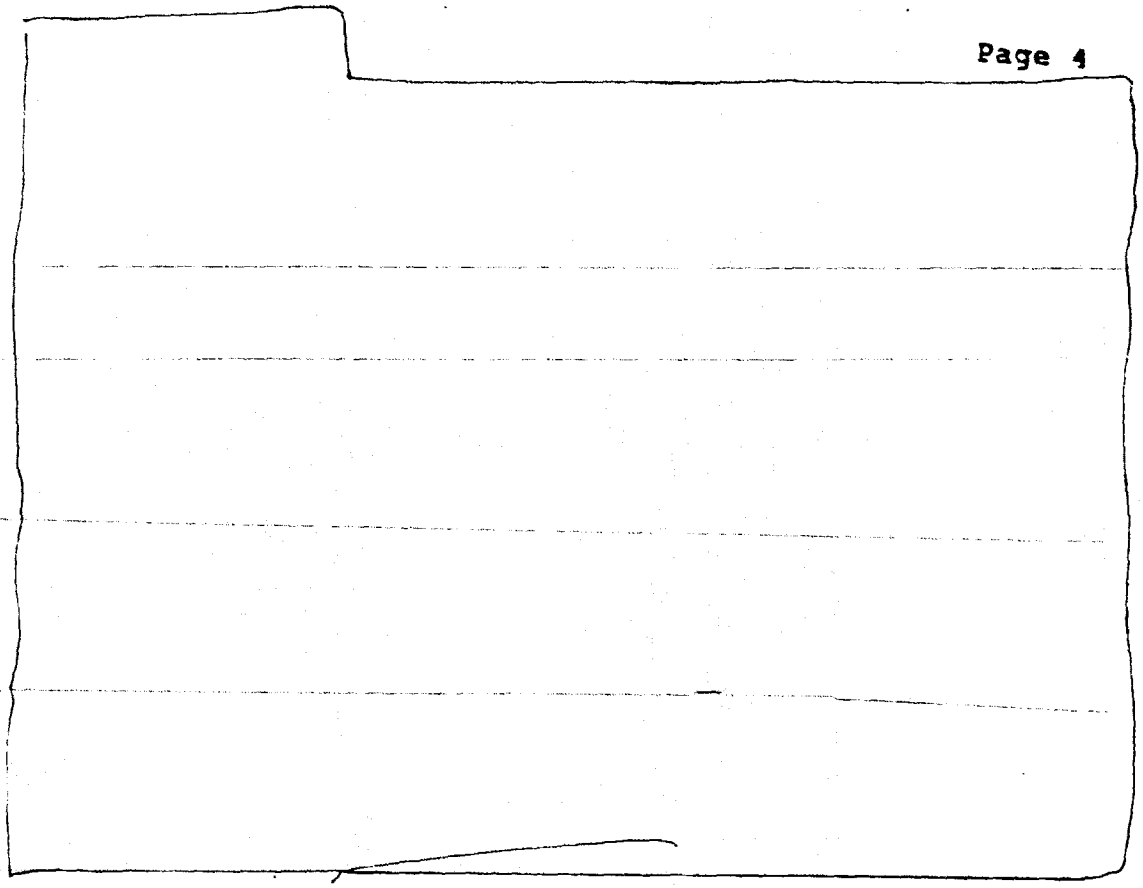
Abbott's NDA 18-801 is approved for marketing Sterile Water for Injection in 10 mL, 20 mL, and 50 mL plastic vials. You should submit a supplement to NDA 18-801 for approval of Sterile Water for Injection in the new plastic syringe.

g. Verapamil Hydrochloride Injection, USP, 2.5 mg/mL

You currently have approved ANDAs for Verapamil Hydrochloride Injection, USP, 2.5 mg/mL in glass vials, glass ampules, and glass syringes. If you intend to replace the glass syringe with the new plastic syringe you may submit a supplement for the new container closure system to the ANDA for the glass syringe. If you intend to add the product packaged in the new plastic syringe to your existing product line, you must submit a new ANDA.

2. Products for which Abbott does not have approved NDAs or ANDAs but for which a reference listed drug exists:

3. Products for which there is no approved reference listed drug:



The applications in group three would be expected to be subject to user fees under the PDUFA.

If you have any questions with respect to these recommendations, please contact Dr. Marilyn Apfel at (301) 594-5460.

Sincerely,

/S/

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

November 6, 1998

Thomas F. Willer, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537

Dear Dr. Willer:

This letter is in response to your inquiry regarding the regulatory requirements that should be followed to gain marketing approval for changing certain parenteral drug products from glass to plastic syringe containers. See also the attached letter dated September 3, 1996, in which Roger Williams, M.D. addressed a similar matter for your attention.

After careful consideration, we have the following observations:

1. Drug products contained in plastic are deemed by regulation to be "new drugs". See 21 CFR 310.502 (a) (10) and 310.509 (a). The "new drug" status of parenteral drug products in plastic containers applies to both large and small volume products. Id.; see also CDER MAPP 6020.2 "Applications for Parenteral Products in Plastic Immediate Containers" (copy of MAPP enclosed).

2. As "new drugs", such products can only be introduced or delivered for introduction into interstate commerce if they are the subject of an approved application filed under section 505(b) or 505(j) of the Federal Food, Drug and Cosmetic Act.

3. For each of the products under discussion, an abbreviated application may be filed under section 505(j) if a "listed drug" as defined in section 505(j)(7) can be identified for the drug product. It is our understanding that there are no "listed drugs" for the products you are seeking to market.

4. Therefore, to gain the necessary market approval for the drug products under discussion, you would be expected to file an application under section 505(b) of the Act. Based on your description of the products, including the apparent substantial marketing history, you should consider whether an application under section 505(b)(2), which may sometimes may consist of simple literature/medical textbook

information to support safety and efficacy, may be feasible for each of these drug products.

If you have any questions or comments concerning this matter please contact Ms. Patricia DeSantis, Drug Review Program Director, by phone at (301) 594-5400.

Sincerely,

/S/

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

Enclosures

REVIEW MANAGEMENT

APPLICATIONS FOR PARENTERAL PRODUCTS IN PLASTIC IMMEDIATE CONTAINERS

CONTENTS

PURPOSE This MAPP describes the types of new drug application that will satisfy the requirements in 21 CFR 310.509(a) for a new drug application for approval of any parenteral drug product to be packaged in a plastic immediate container.

BACKGROUND

The Code of Federal Regulations, Title 21, Section 310.509(a) established that any parenteral drug product packaged in a plastic immediate container is a new drug under section 201(p) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and requires an approved new drug application as a condition for marketing. Section 310.509 took effect when 505(b) was the only provision in the FD&C Act for submission of a new drug application. The subsequent enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (Waxman-Hatch Amendments) replaced 505(b) with 505(b)(1), 505(b)(2) and 505(j), thereby creating three distinct types of applications for approval of new drugs depending on the nature and the source of the evidence required to demonstrate the safety and effectiveness of the new drug product.

REFERENCES

- 21 CFR 310.509 Parenteral Drug Products in Plastic Containers
- 21 CFR 314.3 Definitions

DEFINITIONS

- **Application.** As defined under 21 CFR 314.3, includes all amendments and supplements to the application.
- **Parenteral Drug Product.** A sterile solution intended for administration by injection, internal irrigation, or for use in dialysis procedures.
- **Small Volume Parenteral** (SVP). A parenteral drug product packaged in a volume of less than 100 mL.
- **Large Volume Parenteral** ((LVP). A parenteral product packaged in a volume of 100 mL or more.
- **Limited Confirmatory Testing.** Simple studies intended to rule out unlikely problems. In some cases limited confirmatory testing may include acute animal studies. However, a study to answer basic safety or effectiveness questions or a study that would require substantial scientific review would not be considered limited confirmatory testing.

POLICY

- The requirements for a "new drug application" under 21 CFR 314.509(a) may be satisfied by a new drug application (NDA) submitted in accordance with section 505(b)(1) or section 505(b)(2), an abbreviated new drug application (ANDA) submitted in accordance with section 505(j) or, for antibiotics, an NDA or abbreviated antibiotic application (AADA) submitted in accordance with section 507 of the FD&C Act, or by a supplement to a previously approved application of one of these types.
- An application for approval of a parenteral product in a plastic immediate container may be filed as an ANDA under section 505(j) or, for antibiotics, an AADA under section 507 provided that, 1) the product duplicates an approved product listed in the current edition of *Approved Drug Products with Therapeutic Equivalence Evaluations* ("The Orange Book") and 2) approval of the product in the plastic immediate container does not require studies beyond limited confirmatory testing and the testing described in the USP.
- An application for approval of a parenteral product in a plastic immediate container for which the container requires animal studies beyond limited confirmatory testing and the testing described in the USP to show that the drug

product is safe must be submitted as an NDA under section 505(b) or, for antibiotics, under section 507.

- An application for approval of a parenteral product in a plastic immediate container containing an active ingredient or a combination of active ingredients not previously approved under an application submitted under section 505(b) or section 507, including an application for a product currently marketed in a glass container for which there is no reference listed drug, should be filed as an NDA under section 505(b) or 507 (as appropriate).

  1. Applications filed for approval of new drugs under 505(b) and non-abbreviated applications under 507 are required to contain evidence of safety and effectiveness. Published reports may be adequate for certain applications. However, reference to general recognition of safety and effectiveness is an inadequate basis for approval of a new drug.

  2. Applications filed under 505(b) or 507 for parenteral products in plastic containers that meet the definition of a "human drug application" in the Prescription Drug User Fee Act of 1992 (PDUFA) are subject to user fees.

- This policy applies to both large volume parenteral products and small volume parenteral products.

- This policy applies to applications for parenteral products packaged in plastic immediate containers regardless of whether the plastic material has been previously used to package an approved drug product.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

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MEDICAL LITERATURE REFERENCES

10% Calcium Chloride

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Calcium Chloride: Reassessment of Use in Asystole

Harlan A Stueven, MD*† / Bruce M Thompson, MD*‡ / Charles Aprahamian, MD*‡ / Denis J Tonsfeldt, MD*† / Milwaukee, Wisconsin

Calcium chloride has been advocated since the 1920s for resuscitation of asystole and ventricular fibrillation. Most reports have been anecdotal, and have failed to substantiate its effectiveness. In two large retrospective series with a collective experience of 181 patients, investigators reviewed the effectiveness of calcium chloride in asystole and did not support its use. A prospective, randomized, double-blind study comparing calcium chloride with saline in the prehospital setting was done. Patients with trauma or pediatric arrests were excluded. During the period from October 1982 to October 1983, a total of 32 patients with witnessed arrests presented with a rhythm of asystole and were refractory to epinephrine, bicarbonate, and atropine. The rate of successful resuscitation in the calcium group was 5.6% (1/18), and there were no successful resuscitations (0/14) in the saline group (P = .37). A successful resuscitation was defined as conveyance of a patient with a rhythm and pulse to an emergency department. Groups were analyzed for sex, age, cardiac history, and cardiac drugs, and there were no statistically significant differences. No patient who was successfully resuscitated in the field was discharged alive from the hospital. Calcium chloride is of no value in resuscitating refractory asystole in the prehospital cardiac arrest setting. [Stueven HA, Thompson BM, Aprahamian C, Tonsfeldt DJ: Calcium chloride: Reassessment of use in asystole. Ann Emerg Med September 1984 (Part 2);13:820-822. Key words: bradyasystolic arrest; calcium chloride.]

Introduction

Calcium chloride is advocated by the American Heart Association for the resuscitation of asystole. This recommendation appears to be based on in vitro studies performed by Ringer[1] in 1882; animal studies reported by Wiggers[2] in 1930; dog studies reported by Hooker, Kouwenhoven, and Langworthy[3] in 1933; anecdotal experience in human patients reported by Beck and Mautz[4] in 1937; and finally human cases reported by Kay and Blalock[5] in 1951. None of these early studies specifically looked at the type of rhythm with which the patient presented and whether the patient was in cardiac standstill and/or ventricular fibrillation. Nonetheless the consensus to date seems to be that "calcium chloride may be life saving in the treatment of cardiac standstill arising spontaneously or following the successful defibrillation of a heart in ventricular fibrillation."[5] Recently, however, the use of calcium in this setting has been questioned.

Historical Perspectives

In 1882 Professor Ringer from the University College, London, conducted experiments on an in vitro ventricle. He recorded its electrical activity in response to a saline solution prepared with distilled water. Much to his chagrin, he later found that the distilled water was actually pipe water from the New River Water Company, and that it contained a number of cations and anions, including calcium, magnesium, sodium, and potassium. He set about to test each ion for its potential effect on the ventricle. Interestingly he found that pure saline slowly allowed the heart to become anelectric, but that with the addition of minute amounts of pure "anhydrous" calcium chloride (one part per 1,082), he was able to reproduce his previous findings of the heart continuing to beat for more than four hours. His conclusion was that "a perfect contraction can be obtained with neutral fluid composed of saline with a minute trace of calcium chloride and potassium chloride."[1]

During the ensuing years there was a hiatus in our advancement of knowledge about cardiac physiopharmacology. Clinical reports began appearing in the late 1920s on use of potassium salts, calcium chloride, and epinephrine in resuscitation of ventricular fibrillation. The effect of potassium apparently was to arrest the heart and create asystole; calcium chloride was then injected, the heart was allowed to rest for one minute, and gentle massage allegedly restored the heartbeat. A summary of studies on calcium chloride use in asystole is shown (Table). Wiggers[2] reported that in dogs fibrillation could be abolished by intravenous administration of 5 cc of 5% potassium chloride, and that calcium chloride administration (1 cc/kg of a 5% solution; or 50 mg/kg, equivalent to 3.5 g in a 70-kg person) could restore a coordinated beat with the assistance of manual cardiac massage.

Hooker and colleagues[3] studied the effect of alternating electrical currents on canine ventricular fibrillation. Each dog was induced into ventricular fibrillation by house current, was countershocked, and one minute later one group received an injection of 2 cc adrenaline (1:1,000) and 50 cc

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TABLE. *Use of calcium chloride in asystole*

Author	No. Subjects	Rhythm: Initial	Rhythm: Before Calcium	Calcium Dose	Successful Resuscitation	Statistics
Animal Studies						
Wiggers[2] (1930)	Dogs	VF	Asystole	250-300 mg	Effective with massage only	None
Hooker[3] (1932)	Dogs	VF	Unknown	a) 230 mg b) None	6/11 5/11	None
Redding[5] (1963)	Dogs	Asystole	Asystole	200 mg	6/10	Inferior to epinephrine $P<.05$
Anecdotal Report						
Kay[6] (1951)	4	3 EMD	Unknown	250-400 mg	4	None
Retrospective Studies						
Stueven[10] (1983)	129	Asystole	Presumed asystole	a) 0.5-1.0 g b) No calcium	8/105 (8%) 8/24 (33%)	$P<.002$
Harrison[11] (1983)	52	Variable	Asystole	a) 1 g b) No control	0	
Prospective Study						
Stueven	32	Variable	Asystole	a) 0.5 g b) No calcium	1/18 0/14	$P = .37$

VF = ventricular fibrillation.
EMD = electromechanical dissociation.
Successful resuscitation = conveyance to ED with pulse and rhythm.

calcium chloride 0.046% (230 mg) in 0.9% sodium chloride with heparin and another group received Ringer's. Although their study was intended to review the effect of countershock, they found that six of the 11 dogs that received the combination salt solution, versus five of 11 that did not receive calcium, were resuscitated successfully.

Kay and Blalock[6] reported on four patients given calcium and epinephrine for cardiac arrest. All arrests occurred during cardiac surgery and all were in children (three of whom were less than 18 months old). The course of other drugs given during resuscitation, especially epinephrine, is not delineated clearly in all cases, and potential interaction of other drugs was not considered. Yet their conclusion was that, "Calcium chloride may be life saving in the treatment of ventricular standstill arising spontaneously or following the successful defibrillation of a heart in ventricular fibrillation."[6]

More Recent Studies

In 1963 Redding and Pearson[5] published results of dog experiments evaluating resuscitation from asphyxial asystole. Of ten dogs that received only intracardiac calcium chloride (200 mg), circulation was restored in six. The authors concluded that, "Calcium chloride was intermediate in effectiveness but significantly inferior to epinephrine ($P < .05$) in restoring circulation."[5]

In 1974 the American Heart Association proposed standards for cardiopulmonary resuscitation and emergency cardiac care. Those standards included the use of calcium chloride in the treatment of asystole. Since that time, potentially adverse effects associated with the use of calcium chloride have been reported.

Dembo[7] followed the American Heart Association standards and gave arrest patients 5 cc of 10% calcium chloride. After five minutes, measured serum calcium levels ranged from 12.9 to 18.2 mg/dL, with a mean of 15.3 mg/dL. Mean serum calcium levels did not fall to normal until 15 minutes had passed. Perhaps these dangerously high serum calcium levels increase cellular damage.[7]

Current Clinical Studies

With such controversy surrounding the use of calcium chloride for asystole, we undertook a retrospective study of the use of calcium in prehospital cardiac arrest. In our 129 patients initially presenting in asystole, only eight of 105 (8%) of the patients who received calcium (0.5 to 1.0 g) were resuscitated successfully, while eight of 24 (33%) in the no-calcium group were resuscitated successfully ($P < .002$). That study led us to conclude that, "The use of calcium in the prehospital setting, in currently recommended dosages for cardiac arrest with initial arrest rhythm of asystole, is highly suspect."[8]

Similarly Harrison and Amey[9] reported on their paramedic prehospital experience with calcium chloride. Of 52 cardiac arrest patients who were in asystole when calcium was administered, six developed a rhythm change but none developed a pulse. All patients had received sodium bicarbonate and epinephrine. It became clear that a prospective, randomized, double-blind study was needed to assess the effectiveness of calcium chloride for asystole.

To that end we carried out such a study, comparing calcium chloride to saline in a prehospital setting. Patients with trauma and pediatric arrests were excluded. From October 1982 to October 1983, a total of 32 patients with wit-

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nessed arrests presented with a rhythm of asystole and were refractory to epinephrine, bicarbonate, and atropine. All patients were intubated and had an intravenous line started. The rate of successful resuscitation in the calcium group was one of 18 (5.6%) while none in the saline group was resuscitated successfully ($P = .37$). A successful resuscitation was defined as conveyance of a patient with a rhythm and pulse to an emergency department. Groups were analyzed for sex, age, cardiac history, and cardiac drugs, with no statistically significant differences. No patient who was successfully resuscitated in the field was discharged alive from the hospital.

Conclusions

The literature supporting the use of calcium chloride for asystole has been reviewed and found to be largely anecdotal. Two large retrospective studies have not supported the use of calcium chloride for asystole, and our prospective, randomized, double-blind comparison study failed to substantiate the effectiveness of calcium chloride for asystole. Thus the use of calcium chloride in prehospital cardiac arrest in currently recommended dosages for refractory asystole is not supported, and probably should be deleted from the American Heart Association's advanced cardiac life support guidelines.

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Developments in Transcutaneous and Transthoracic Pacing During Bradyasystolic Arrest

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Transthoracic cardiac pacing historically has been relegated to the role of the technique of last resort in treating cardiac arrest. Recent studies have shown that this technique has a high rate of successful electrical capture, but often without mechanical activity. Survival rates have been shown to be dismal when the technique is used late in cardiac arrest. Results of several recent studies of patients paced by the transcutaneous technique have suggested that electrical capture can often be rapidly obtained in asystolic or pulseless bradycardic patients. Even though electrical capture can occur late in a cardiac arrest, the development of mechanical activity with survival is rare. Survivors generally have been treated early in their arrest and have had hemodynamically ineffective bradycardias. These findings suggest that rapid initiation of transcutaneous pacing in patients with Stokes-Adams attacks, increasing heart block associated with myocardial ischemia, postdefibrillation asystole, or pulseless bradycardia may improve survival. However, victims of a prolonged cardiac arrest whose myocardium has irreversibly ceased to function mechanically are unlikely to benefit from any pacing technique. [Hedges JR, Syverud SA, Dalsey WC: Developments in transcutaneous and transthoracic pacing during bradyasystolic arrest. Ann Emerg Med September 1984 (Part 2);13:822-827. Key words: bradyasystolic arrest; pacing techniques.]

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Introduction

Asystole and hemodynamically ineffective bradycardias are rhythms commonly paced during cardiac resuscitation. Traditionally cardiac pacing has been used as the last resort following failure of pharmacologic therapy with use of atropine, epinephrine, isoproterenol, or dopamine. The use of these drugs may not be harmless in that they have the po-

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PHARMACOLOGY OF PEDIATRIC RESUSCITATION

H. Michael Ushay, MD, PhD, and Daniel A. Notterman, MD

The pharmacology of pediatric resuscitation continues to evolve and remain an active area of investigation. This continuing investigation is caused by the dismal outcome of cardiopulmonary arrest, from the perspective of the few children who can be resuscitated to a perfusing rhythm and the neurologic devastation frequently present in long-term survivors. The current guidelines published in 1992 by the Emergency Cardiac Care Committees of the American Heart Association and the American Academy of Pediatrics[1] place increased emphasis on the need to interrupt the chain of events leading to cardiac arrest. This emphasis includes close attention to oxygen supply and delivery, airway maintenance, and rapid attainment of secure vascular access. After these elements are ensured, pharmacologic adjuncts come into play. Major recent pharmacologic changes include the addition of high-dose epinephrine for cardiac arrest and the greater reliance placed on epinephrine for treatment of hypotension and bradycardia. The roles of calcium and sodium bicarbonate are debated, but in general their use is de-emphasized except in specific circumstances. This article reviews the current trends in pediatric resuscitation pharmacology, with an emphasis on areas of controversy and recent developments. Excellent and in-depth reviews of the subject are available.[1, 15, 16]

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CAUSES AND EPIDEMIOLOGY OF CARDIAC ARREST IN CHILDREN

Cardiac arrest in children is different than in adults. The cause(s) is not usually a primary cardiac event but rather the end result of inadequate supply of cellular substrate. The most important substrate is oxygen, and its delivery to tissue, a function of the cardiac output and the oxygen content of the blood, can be interrupted at several levels. Cardiac output is decreased in patients with cardiogenic and hypovolemic shock. Inadequate oxygen content from decreased oxyhemoglobin saturation occurs in patients with ventilation-perfusion mismatch and shunt, both intrapulmonary and extrapulmonary. Intrapulmonary shunt may result from pneumonia, pneumothorax, asthma, upper airway obstruction, or asphyxia, as in drowning and closed-space fires. Relative to adults, infants and children have higher rates of oxygen consumption than adults and thus are more susceptible to inadequate tissue-oxygen delivery. Insufficient hemoglobin caused by acute hemorrhage or bone marrow failure also results in inadequate oxygen delivery. Pathophysiologic states, such as systemic inflammatory response and septic shock,[13, 14] result in tissue and organ-bed shunts, which block oxygen delivery at the end-organ level. At the cellular level, carbon monoxide and cyanide poison the oxidative phosphorylation pathways. All of the above, if unchecked, eventually may lead to cardiopulmonary arrest in infants and children.

Purely cardiac events leading to sudden death, although comparatively rare, do occur in children. At less than 1 year of age, sudden death usually is caused by ductus-dependent, complex cyanotic congenital heart disease. After the first year, the most common cardiac causes of sudden death include myocarditis; hypertrophic cardiomyopathy; coronary artery disease, possibly secondary to Kawasaki's disease; congenital coronary artery anomalies, such as anomalous left coronary artery; conduction system abnormalities; mitral valve prolapse; and aortic dissection.[47] Dysrhythmic cardiac arrests may occur secondary to prolonged supraventricular tachycardia (SVT). The prolonged QT syndrome, an anomalous left coronary artery, and congenital cardiomyopathies may lead to ventricular tachycardia and ventricular fibrillation.

Recent retrospective studies have examined the causes and outcomes of pediatric cardiac arrest. Over a 9-year period, 79 children under the age of 16 years had out-of-hosp tal cardiac arrests in a Finnish city of 516,000 population. Sudden infant death syndrome was the leading cause of cardiac arrest, followed by trauma, airway-related events, and (near) drowning. Of the patients considered for resuscitation, asystole was the most common initial rhythm (78.9%), followed by pulseless electric activity (13.5%) and ventricular fibrillation (3.8%). When resuscitation was attempted, the survival rate was 14.7% overall, and 0% when a witnessed arrest was of cardiac origin.[48] In Birmingham, Alabama, of 63 children with out-of-hospital cardiopulmonary arrest who presented to the emergency department of a children's hospital, 60 were pulseless and apneic on arrival, 18 (28.6%) were successfully resuscitated and admitted to the intensive care unit, and 6 (9.5%) were discharged from the hospital. Five of the six survivors had severe neurologic deficits, and one was normal.[34] In Toronto, Ontario, a review of 101 out-of-hospital cardiac and respiratory arrests over a 7.5-year period showed that of the 15 children who survived to hospital discharge, only six were described as normal or mildly neurologically impaired,

four were moderately impaired, and five were severely impaired or vegetative. All of the children who were normal at discharge had a respiratory arrest without a cardiac arrest.[49] These dismal data reinforce the need to prevent, rather than treat, nonperfusing rhythms.

PHARMACOLOGY OF RESUSCITATION

A list of frequently used resuscitation drugs, their preparations, and pediatric dosages is shown in Table 1.

Administration

Until recently, with the rediscovery of intraosseous infusion, the difficulty associated with obtaining vascular access in arrested pediatric patients presented a significant impediment to the administration of drugs during resuscitation. Endotracheal (ET) administration is available for lipophilic agents, such as epinephrine, lidocaine, atropine, and naloxone. The pharmacokinetics of endotracheally administered agents are very variable and are a subject of continuing investigation.[50, 51] In some scenarios, however, such as older children in whom IV access cannot be obtained, there is no alternative to ET administration. The pharmacokinetics of ET administration of cardiovascular drugs has been reviewed in detail by Steinberg and Notterman.[106] Intraosseous (IO) access can be achieved rapidly in pediatric patients and is equivalent in time to onset of action, time to peak effect, and magnitude of effect on blood pressure to that resulting after administration via the central venous route.[85] A major advantage

Table 1. BOLUS DRUGS, STANDARD PREPARATIONS, DOSAGES, AND MAXIMUM SINGLE DOSES

Drug	Dosage	Maximum Single Dosage
Epinephrine, standard dose (1:10,000)	0.01 mg/kg (0.1 mL/kg)	10 mL
Epinephrine, high dose* (1:1000)	0.1 mg/kg (0.1 mL/kg)	10 mL
Calcium Chloride 10%† (100 mg/mL)	20 mg/kg (0.2 mL/kg)	10 mL
Atropine (0.1 mg/mL)	0.01 mg/kg (0.1 mL/kg) Minimum dose 0.1 mg	10 mL 1 mL‡
Sodium Bicarbonate 8.4% (1 mEq/mL) Use half strength in neonates	1 mEq/kg (1 mL/kg)	50 mL
Dextrose 25% (0.25 g/mL)	0.5 g/kg (2.0 mL/kg)	100 mL
Lidocaine (20 mg/mL)	1 mg/kg (0.05 mL/kg)	5 mL
Bretylium (50 mg/mL)	5 mg/kg (0.1 mL/kg)	0.2 mL/kg

*For second and subsequent doses for asystolic or pulseless arrest, or for endotracheal administration.

†Rapid push induces bradycardia.

‡Minimum volume to administer.

of the IO route is that volume resuscitation and continuous infusions of vasoactive agents can be administered. The current guidelines of the American Heart Association state that if peripheral intravenous (IV) access cannot be established within three attempts or 90 seconds, intraosseous access should be obtained. Any IV or IO access is preferable to ET administration, and medications given by the ET route should be re-administered when vascular access is obtained. The relevant anatomy, indications, contraindications, and techniques have been reviewed.[36] The intraosseous route is not just for patients in cardiac arrest. It should be considered whenever a life-threatening illness requires immediate drug therapy. The IO route is safe and effective, albeit with occasional complications.[72]

Pharmacologic Agents

Epinephrine

Epinephrine is the primary resuscitation medication. It is indicated for patients with cardiac arrest, symptomatic bradycardia unresponsive to ventilation and oxygen administration, and hypotension not related to volume depletion. It has achieved new prominence in superseding atropine and isoproterenol for treatment for patients with symptomatic bradycardia.[34]

Pharmacology. Epinephrine is an endogenous catecholamine produced in the adrenal medulla. Epinephrine activates α-, β_1-, and β_2-adrenergic receptors. At very low concentrations of epinephrine (infusion rates of 0.05 to 0.20 μg/kg/min), the β-adrenergic receptors are preferentially activated. Activation of the β_1-receptor in the myocardium and conducting system results in increased heart rate, decreased systolic time interval, and augmented contractility. Stimulation of the peripheral β_2-receptors relaxes resistance arterioles, causing systemic vascular resistance and diastolic blood pressure to decrease. As systemic vascular resistance decreases, a reflex tachycardia is superimposed on the direct chronotropic effect of β_1-receptor stimulation. As the dosage and, hence, concentration of epinephrine increases (infusion rates of 0.5 to 2.0 μg/kg/min), activation of vascular α-adrenergic receptors begins to predominate, resulting in increased systemic vascular resistance and blood pressure.[80]

The elimination half-life of epinephrine is approximately 2 minutes. It is methylated by catechol-O-methyl transferase (COMT) to metanephrine in the liver and kidneys or deaminated by the action of monoamineoxidase to 3,4-dihydroxyphenylglycoaldehyde. The O-methylated amine and the glycol then may be conjugated to sulfate or glucuronide and excreted in the urine.[40] In healthy adults, clearance is 35 to 89 mL/min/kg (2.1 to 5.3 L/h/kg).[11, 26] The wide interindividual variation in clearance in healthy adults would be expected to be more pronounced in critically ill infants and children. No information is available about the pharmacokinetics of epinephrine in cardiac arrest. In critically ill children receiving epinephrine at dosages from 0.03 to 0.2 μg/kg/min, plasma concentrations at steady state ranged from 0.67 to 9.4 μg/L and were linearly related to dosage.[37] Clearance values ranged from 15.6 to 79.2 mL/min/kg (0.94 to 4.75 L/h/kg). Epinephrine demonstrated a linear relationship between infusion rate and plasma concentration over the range of dosages

studied. The short 2- to 3-minute half-life of epinephrine indicates the importance of administering epinephrine at least every 3 minutes during cardiac resuscitation. It also suggests the advantage of using a high-concentration epinephrine infusion during resuscitation.

The β-adrenergic effects of epinephrine are of equal importance to α-receptor stimulation in patients with shock and severe myocardial dysfunction. In this circumstance, augmentation of contractility and blood pressure is required. In patients with cardiac arrest, however, the α-adrenergic effect is considered most important. The increase in systemic vascular resistance caused by α-receptor activation raises aortic diastolic pressure, which in turn increases flow through the coronary arteries and the myocardium. Perfusion occurs during the relaxation phase of the chest-compression cycle. The difference between the aortic diastolic pressure and the central venous pressure during relaxation is termed the *coronary perfusion pressure*.[78, 80] The coronary perfusion pressure is the most reliable predictor of return to spontaneous circulation in adults.[80] An increase in coronary perfusion pressure above that which can be generated with chest compressions alone is required to obtain return of spontaneous circulation. The coronary perfusion pressure deteriorates in children over time unless epinephrine is administered. The role of increased aortic diastolic blood pressure in resuscitation has led to investigation of direct injection of epinephrine into the peripheral arterial system and into the aortic arch.[74] Aortic arch delivery of epinephrine yielded a faster and greater increase of aortic and coronary perfusion pressures than injection of an equivalent amount into the superior vena cava of mongrel canines. The aortic arch group had a faster return to spontaneous circulation. Clinical trials with this method are underway, but no translation of this work into the pediatric age group has occurred. The rapid application of this technique to out-of-hospital and emergency-department resuscitations of children is extremely difficult but may be feasible in the intensive care unit, where central arterial lines are used frequently.

The role of the β-adrenergic receptor activation of epinephrine in resuscitation is unclear. It has been postulated that increase in chronotropy and inotropy caused by β-adrenergic stimulation may increase oxygen consumption and negates any improvement in myocardial oxygen supply caused by α-adrenergic stimulation and elevation of coronary perfusion pressure. This increase in myocardial oxygen consumption explains the poor results seen in adults with high-dose epinephrine (see subsequent discussion) and has led to the investigation of drugs with less β-adrenergic activity, such as norepinephrine, or pure α-adrenergic activity, such as phenylephrine or methoxamine, in resuscitation. In large dosages, norepinephrine increased coronary perfusion pressure as effectively as high dosages of epinephrine.[79] One study comparing epinephrine with norepinephrine in adults with ventricular fibrillation suggested that norepinephrine restores circulation more effectively.[67] A randomized trial comparing high-dosage epinephrine, standard-dosage epinephrine, and norepinephrine showed no advantage to norepinephrine compared with high-dosage epinephrine.[77] In work that may be more relevant to the pediatric population, norepinephrine had no advantage versus epinephrine in an asphyxial-arrest model.[58] Despite the lack of β-adrenergic activity, phenylephrine has shown no advantage over epinephrine in animal studies.[67] Methoxamine, a relatively specific α_1-receptor adrenergic agonist, also has been studied. Two double-blind studies comparing epinephrine with methoxamine in adults with electromechanical dissociation failed to show

any benefit from methoxamine.[84, 114] In another randomized, double-blind comparison of methoxamine and epinephrine in adult human cardiopulmonary arrest, no difference was seen in the initial rate of resuscitation, survival to hospital discharge, and eventual neurologic status when 2 mg every 4 minutes of epinephrine was compared with 40 mg methoxamine.[87] In a swine fibrillation model, epinephrine produced significantly better myocardial blood flow, myocardial oxygen utilization, cerebral blood flow, and defibrillation success rates than did methoxamine.[18] The lack of obvious improvement in results with the pure α agents has led some investigators to consider that the increase in cerebral perfusion seen with epinephrine may be caused, at least in part, by β-receptor–induced vasodilation of the cerebral vasculature.[6]

Dosage and Administration. The recommended initial IV or IO dose of epinephrine for asystolic or pulseless arrest and for symptomatic brachycardia (with a pulse) unresponsive to oxygen and adequate ventilation is 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution). The dose for endotracheal administration is 0.1 mg/kg (0.1 mL/kg of a 1:1000 solution). The second and subsequent doses of epinephrine for asystole or pulseless arrest by all routes should be 0.1 mL/kg of a 1:1000 solution. The major change in dosage recommendation for epinephrine is the addition of high-dose epinephrine.

It is known from animal studies that much more epinephrine than the usually recommended dosage of 10 μg/kg is necessary to generate and maintain an increased diastolic blood pressure in the face of cardiac arrest.[78] Other studies showed that doses of epinephrine 10 to 20 times larger than those recommended at the time yielded greater increases in brain and heart blood flow.[17] In clinical trials, higher coronary perfusion pressures were measured in adults with prolonged arrest using higher epinephrine dosages.[48] The use of high-dosage epinephrine (0.2 mg/kg) resulted in return of spontaneous circulation in six of seven children with bradyasystolic cardiac arrest who had failed to respond to two standard (0.01 mg/kg) doses.[44] In a subsequent report, 70% (14 of 20) of children receiving 0.2 mg/kg epinephrine after failing to respond to two 0.01-mg/kg doses had return to spontaneous circulation versus none of a historically controlled standard-dosage group. Eight of fourteen survived to discharge, and at follow-up, three were reported as neurologically asymptomatic.[43] Because the outcome of asystolic and pulseless arrest in children is poor and a beneficial effect of high dosages of epinephrine was observed in animal studies and in these pediatric trials, the American Heart Association recommends that second and subsequent dosages for unresponsive asystolic and pulseless arrest should be 0.1 mg/kg (0.1 mL/kg of 1:1000 solution). The higher dosages of epinephrine should be administered within 3 to 5 minutes following the initial dose and should be repeated every 3 to 5 minutes during resuscitation. The 1:1000 solution is recommended to avoid the high volumes required if the 1:10,000 solution is used for the 0.1 mg/kg dosing. The use of the 1:1000 solution also prevents potential problems related to toxic doses of the preservatives contained in the solutions being administered. The recommendations also suggest that in ongoing resuscitation, a continuous infusion of epinephrine of up to 20 μg/kg/min may be administered until resumption of cardiac activity.

Simultaneous with publication of the American Heart Association guidelines listing high-dosage epinephrine as an option in cardiac arrest resuscitation, the results of two large (1280 and 650 patients) randomized and blinded studies comparing standard-dosage epinephrine with high-dosage epinephrine in adults

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were published.[19, 107] Neither showed any difference in the overall rate of return of spontaneous circulation, survival to hospital admission, survival to hospital discharge, or neurologic outcome between the two groups. In the study of out-of-hospital arrest, no adverse effects of high-dosage epinephrine were found; however, in the study of Stiell and colleagues,[107] evidence showed that patients who received their first dose of epinephrine more than 10 minutes after arrest had a statistically significant poorer chance of resuscitation with high-dosage epinephrine than with standard-dosage epinephrine. A comparison of standard-dosage epinephrine (0.02 mg/kg) with high-dosage epinephrine (0.2 mg/kg) in a prolonged (15-min) swine fibrillatory arrest model showed no improvement in 24-hour survival and more early mortality in animals receiving high-dosage epinephrine. Both dosages raised the coronary perfusion pressure equal amounts. Most of the animals who were resuscitated with high-dosage epinephrine exhibited severe tachycardia and hypertension that, in some instances, may have contributed to the increased early mortality.[10] The apparent lack of success of high-dosage epinephrine in three human adult and the one animal study described earlier was attributed to the effects of β_1-receptor–induced tachycardia and inotropy, causing increased myocardial oxygen consumption and perpetuation of myocardial ischemia in a heart that, in most cases, had significant coronary artery disease. The concentration of epinephrine in the circulation at the time of resuscitation was much greater in the high-dosage cohorts, and consequently the deleterious side effects were greater. Recent animal studies have supported the theory that high concentrations of epinephrine remaining in the bloodstream and tissues after resuscitation are harmful. In a comparison of epinephrine, phenylephrine, and epinephrine plus the β-blocker esmolol using a rat model of fibrillatory cardiac arrest, the epinephrine group had significantly worse postresuscitation myocardial dysfunction and duration of survival than did the phenylephrine or epinephrine plus esmolol groups.[111]

The pediatric evaluation of high-dosage epinephrine is not complete, but a 48-month retrospective cohort study of high-dosage epinephrine in pediatric out-of-hospital cardiopulmonary arrest involving 65 patients, 40 of whom received high-dosage epinephrine, has been published.[29] No difference was found in return of spontaneous circulation or electric activity between the two groups. Children may tolerate high-dosage epinephrine better than adults because they generally lack coronary artery disease and better tolerate tachycardia. The effort to increase coronary perfusion, which should be relatively easy in nonatherosclerotic pediatric hearts, has not yielded consistently more success in pediatric resuscitation. Historically, most research on cardiac resuscitation has used adult animal models in which ventricular fibrillation is induced, usually by electric stimulation. A randomized, blinded study comparing standard dose (0.02 mg/kg) with high-dose epinephrine (0.2 mg/kg) is a swine model of pediatric asphyxial cardiac arrest has recently been published. There was a tendency for greater return of spontaneous circulation in the high-dose epinephrine group; however, the 2-hour and 24-hour postresuscitation survival rate and neurologic outcome were unchanged between high-dose epinephrine and standard dose epinephrine cohorts. High-dose epinephrine is described as resulting in a "lethal hyperadrenergic state" that contributed to a higher rate of post return of spontaneous circulation mortality.[105] More research is necessary using models of hypoxic arrest to mimic the pediatric situation more closely.

Calcium

Calcium is used less frequently in resuscitation than in the past, when calcium infusion was used to treat electromechanical dissociation (now called *pulseless electrical activity*). Now it is reserved for documented hypocalcemia, hyperkalemia (not cased by digitalis toxicity), hypermagnesemia, and calcium channel blockade. The impetus to avoid excessive administration of calcium is the observation that cytoplasmic calcium accumulation is associated with the cellular response to ischemia. Although the use of calcium infusion is less common than in the past, treatment of hypocalcemia may result in improved hemodynamic function in compromised children.

Pharmacology. Calcium is the major extracellular divalent cation. In plasma, calcium circulates in a concentration of about 8.5 to 10.4 mg/dL (2.1–2.6 mM). Of this amount, approximately 55% is bound to plasma proteins or primarily albumin or complexed with anionic buffers, such as citrate and phosphate. The remaining "ionized" fraction exerts physiologic effects. The normal ionized calcium concentration is approximately 1.12 mM to 1.32 mM, and it is affected by plasma pH and albumin concentration. Acidosis increases the fraction of ionized calcium present, whereas alkalosis lowers it. A decrease in serum albumin concentration may result in a decrease in total serum calcium, but the ionized calcium concentration may remain normal because a smaller portion is protein bound. Conversely, the ionized calcium concentration may remain low, although the total serum calcium may increase with increased albumin.

Septic shock and blood transfusion have been associated with alterations in ionized calcium concentration. Children in septic shock may demonstrate a decrease in ionized calcium concentration despite a normal total calcium level.[24, 129] Serum ionized calcium also may fall after administration of blood preserved with citrate-phosphate-dextran. Positive inotropic effects of calcium following cardiac arrest were documented initially in cardiovascular surgery patients after cardiopulmonary bypass.[108]

Calcium is essential to excitation-contraction coupling and for conduction in certain regions of the heart, particularly the atrioventricular (AV) node. When cardiac muscle is stimulated, calcium enters the cytoplasm and induces actin-myosin coupling, which is terminated when calcium actively is pumped from the cytoplasm. Normally, calcium administration yields increased contractility. In patients with ischemia, however, energy stores may be depleted, resulting in compromise of the pumping mechanisms and cytoplasmic accumulation of calcium, which may lead to cell death.

Calcium is responsible for the initiation of contraction in vascular and other smooth muscle, and it carries an important fraction of depolarizing currents in these tissues.

Calcium administration usually results in increased force of myocardial contraction. Calcium may increase or decrease systemic vascular resistance. In normal hearts, calcium's positive inotropic and vasoconstrictive effects produce a predictable increase in blood pressure.[103]

Dosage and Administration. Calcium chloride and calcium gluconate effectively correct hypocalcemia, provided equivalent amounts of calcium are administered. Calcium chloride ($CaCl_2{\cdot}2H_2O$) is 27.2% by weight calcium. The commercially marketed 10% solution, therefore, delivers 27.2 mg/mL (1.36 mEq/mL). Calcium gluconate 10% solution contains 9.0 mg/mL of elemental calcium. Thus, the dose and volume of calcium gluconate must be three times that of calcium chloride to deliver equivalent amounts of calcium. Calcium chloride is used most frequently in critically ill children and adults and in one study produced consistently higher and more predictable levels of elemental calcium.[50] The current recommended dose is 5 to 7 mg/kg of elemental calcium (20–25 mg/kg of calcium chloride salt). A dose of 0.2 to 0.25 mL/kg of a 10% solution of $CaCl_2$ will deliver this amount of calcium. Injection of $CaCl_2$ into a peripheral vein is accompanied by vasodilation and cutaneous burning. It can sclerose peripheral veins and produce severe chemical burns if it infiltrates into surrounding tissue. In general, the administration of calcium salts through central venous catheters is well tolerated and associated with fewer complications than is injection into a peripheral vein. The rate of administration should be slow to minimize burning, induced slowing of the heart rate, and any drop in blood pressure related to peripheral vasodilatation. The first dose of calcium should be administered no faster than 100 mg/min. Rapid administration of calcium may induce profound bradycardia. Particular care should be taken in patients on digoxin in whom calcium administration may cause a severe dysrhythmia. Calcium forms an insoluble precipitate in the presence of sodium bicarbonate. Because repeated doses of calcium increase the risk of morbidity, the dose should be repeated only if calcium deficiency is present.

Sodium Bicarbonate

The most controversial and debated resuscitation drug is sodium bicarbonate. During cardiopulmonary arrest, a mixed respiratory and metabolic acidosis develops. The longer the arrested state, the more profound the acidosis. Ventilatory failure results in carbon dioxide retention (i.e., hypercarbia) and causes a respiratory acidosis that is present intracellularly and in the plasma. During cardiopulmonary resuscitation, ongoing ischemia induces the myocardial intracellular P_{CO_2} to increase to as much as 300 mm Hg (40 kPa) which is accompanied by a decrease in intracellular pH to below 6.5.[37, 117] The intracellular acidosis from hypercapnia causes diminished contractile performance and increased end-diastolic pressure.[109, 118] Cellular hypoxia also induces a transition to anaerobic metabolism with generation of lactic acid and resulting lactic acidosis. Metabolic acidosis is further exacerbated by decreased renal perfusion in the prearrested and arrested states, resulting in the inability of the body to clear the acid byproducts of intermediate metabolism. During any low-flow, shock state and especially in cardiac arrest, a substantial gradient exists between arterial and central venous pH and P_{CO_2}.[1, 121] Because arterial blood gas analysis reflect mainly the pulmonary circulation in low-flow states, the arterial pH and P_{CO_2} can be much closer to normal than those found in the venous circulation, which is considered more representative of the tissue beds.

The most effective means of correcting the mixed metabolic and respiratory acidosis associated with the low-flow state is the re-institution of effective ventilation, followed by restoration of tissue perfusion. In patients not in cardiac arrest, support of ventilation through early intubation and support of the circulation through appropriately guided fluid resuscitation and the use of inotropes and vasopressors can treat patients with acidosis effectively. Epinephrine, a drug known to increase coronary perfusion pressure and thus facilitate return